REMARKS & CONCLUSION

Claims 28-37 were pending. Claims 33-37 are canceled herein without prejudice or disclaimer. Claims 28-32 are amended. New Claims 38 and 39 are added herein. Claims 28-32 and 38-39 are pending.

Change of Correspondence Address

Applicants note that the instant Office Action was mailed to Foley and Lardner LLP. Applicants further note that a Power of Attorney and Change of Correspondence Address (attached) was filed in this application and is listed on PAIR as being entered in the case as of 4/7/06. According to the POA and Change of Correspondence, the attorney of record is now Faegre & Benson LLP and correspondence is to be sent to the address associated with Customer Number 35657. Applicants respectfully request that the Office take note of the Power of Attorney and Change of Correspondence Address and that all future correspondence be addressed to Faegre & Benson LLP, Patent Docketing, 2200 Wells Fargo Center, 90 South 7th Street, Minneapolis, MN 55402-3901.

Claim Amendments

Claim 28(a) is amended to recite, "comparing the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized with the amino acid sequences of the light and heavy chain variable domains of human antibodies." The amendment is supported in the published Specification (No. 20030103979) at least at Paragraph [0022] and Figure 1, which show the comparison of amino acid sequences of light and heavy chain variable domains between murine LL2 and human REI, EU and NEWM antibodies. Paragraph [0067] discloses that the REI and EU sequences were found to exhibit the highest degree of sequence homology to the LL2 FR sequences, "by comparing the murine variable (v) region framework (FR) sequences of LL2 to that of human antibodies in the Kabat database."

Support for the amendment to claim 28(b) to recite, "selecting framework regions from a first human antibody for the light chain and from a second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is

selected from the third human antibody" is discussed below, but may be found in the published Specification at least at Paragraph [0067] and Example 1. The limitation of previous step 28(e) is incorporated into 28(c) to simplify the claim language. The limitation of previous step 28(d) is incorporated into dependent claim 29, as the subject matter of previous claim 29 may now be found in step 28(b).

The amendment to claim 29 is supported in the published Specification at least at Paragraphs [0023] and [0043].

Claim 30 is amended to list the human NEWM antibody as the source of FR4 of the heavy chain variable region. Support for the amendment may be found in the published Specification at least at Paragraphs [0043] and [0067]. Claim 31 is amended to conform to amended claims 28 and 29.

Claim 32 is amended to simplify the claim language and make it consistent with amended claim 28. The amended claim is supported in the published Specification at least at Paragraph [0036].

New Claim 38 is added to recite the method of claim 28, wherein the light chain framework regions are selected from the human REI antibody. Support for the new claim may be found in the published Specification at least at Paragraphs [0022], [0043], [0067], [0098] and in Figure 1 and Examples 1 and 3.

New Claim 39 is added to recite the method of claim 28, wherein the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody. Support for the new claim may be found in the published Specification at least at Paragraphs [0022], [0043], [0067], [0098] and in Figure 1 and Examples 1 and 3.

Claim Rejections – 35 U.S.C. § 112, 1st paragraph

Claims 28-37 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for introducing new matter into the claims. The Action asserted lack of written description support for, "selecting heavy chain framework regions from four different human antibodies and selecting light chain framework regions from four different human antibodies." [Action at pg. 4, 1st paragraph] The Action further asserted a lack of written description support for degrees of residue identities for the framework regions. Although Applicants respectfully

traverse the assertions, in the interest of advancing prosecution claim 28 is amended to delete recitation to any specific degree of residue identity. Claim 28 is further amended to clarify that the framework regions of the light chain are selected from a first human antibody and the framework regions of the heavy chain are selected from a second and third human antibodies, where the heavy chain FR1, FR2 and FR3 residues are selected from the second human antibody and FR4 residues are selected from the third human antibody.

Written description support for the amendment to claim 28 may be found in the published Specification (No. 20030103979) at Paragraphs [0022], [0043], [0067], [0098] and in Figure 1 and Examples 1 and 3, which disclose that the human REI antibody framework regions were selected for the light chain variable region of the humanized antibody, that FR1, FR2 and FR3 of the human EU antibody and FR4 of the human NEWM antibody were selected for the heavy chain variable region of the humanized antibody, into which the corresponding CDR sequences of the antibody to be humanized were inserted.

The Action asserts that, "the disclosure that the selection of the human NEWM for FR4 of the heavy chain was due to lack of X-ray coordinate data for the EU sequence does not provide sufficient direction and guidance to the currently claimed limitations...." The statement is not entirely understood. It appears to suggest that the selection of FR4 from a different human antibody than FR1-FR3 was based upon the lack of X-ray coordinate data only for FR4. However, the published Specification at Paragraph [0043] states that,

> Similarly, antibody EU (VH) sequences can be selected as the computer counterparts for FR1 to FR3 of the mLL2 heavy chain; FR4 was based on NEWM. **As X-ray coordinate data is currently lacking for the EU sequence, NEWM structural data (PDR Code 3FAB) for FRs 1 to 4 can be used**, and amino acid side groups can be replaced to correspond to mLL2 or EU (hLL2) as needed. (emphasis added)

The cited text clearly indicates that X-ray data is missing for all four of the EU framework regions (FR1, FR2, FR3 and FR4). Therefore, selection of FR4 from NEWM could not have been based on the lack of X-ray coordinate data. Otherwise, each of FR1,

FR2, FR3 and FR4 would have been selected from NEWM as the X-ray data was lacking for all of the EU frameworks.

Thus, the lack of X-ray data had nothing to do with the selection of FR1-3 from EU and FR4 from NEWM. The selection of FR1, FR2 and FR3 from EU and FR4 from NEWM was based on the amino acid homology analysis, as was the selection of the REI FR sequences for the light chain variable region. ("In general, the 3-D structure for both the mLL22 and hLL2 mAbs are best modeled by homology." Specification at Paragraph [0043]) See also Specification Paragraph [0067] which states,

> By comparing the murine variable (V) region framework (FR) sequences of LL2 to that of human antibodies in the Kabat data base (Kabat et al., Sequences of Proteins of Immunological Interest, 5th ed., U.S. Department of Health and Human Services, U.S. Government Printing Office, Washington, D.C.), which is incorporated by reference, the human REI (FIG. 1A, SEQ ID NO. 6) and EU (FIG. 1B, SEQ ID NOS. 9 and 8) sequences were found to exhibit the highest degree of sequence homology to the FRs of VK and VH domains of LL2, respectively. Therefore, the REI and EU FRs were selected as the human frameworks onto which the CDRs for LL2 VK and VH were grafted, respectively. The FR4 sequence of NEWM, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 heavy chain.

Applicants respectfully submit that the written description support in the Specification, which provides detailed teachings for how to make and use a humanized antibody incorporating framework region sequences from the light chain of a first human antibody, with FR1-3 selected from the heavy chain of a second human antibody, and FR4 selected from the heavy chain of a third human antibody, is more than adequate to support the scope of the amended claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 U.S.C. § 112, 2nd paragraph

Claim 31 is amended as suggested by the Action. Claim 28, step (e) is deleted. Claim 33 is deleted. Claim 28(b) is amended to refer to a first, second and third human antibodies to clarify which human antibody is referred to. Claim 32 is amended to more consistently refer to the "at least one vector" of 32(e). Claim 28 is amended to clarify that both the heavy and light chain variable domains of the monoclonal antibody are

humanized, by incorporating the light and heavy chain CDRs of the monoclonal antibody with the corresponding light and heavy chain human framework regions. Claim 37 is canceled and claim 32 is amended to delete the phrase, "A method of producing a humanized monoclonal antibody designed according to the method of claim..." Claim 28 is amended to delete reference to sequence identities of framework regions. Claim 34 is canceled and claim 29 is amended to delete reference to "said framework regions."

Claim Rejections – 35 U.S.C. § 102

Claims 28-23-33 and 37 were rejected under 35 U.S.C. §102 as anticipated by Singer et al. (1993). The Action does not assert, and Singer does not disclose the element of amended claim 28, of "selecting framework regions from a first human antibody for the light chain and from second and third human antibodies for the heavy chain based on the sequence comparison, wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from the third human antibody." Specifically, the Action does not assert that Singer discloses selecting the framework regions for the heavy chain variable region from two different human antibodies, with FR1-3 selected from one human antibody and FR4 selected from another human antibody. Since Singer does not disclose all elements of the amended claims, rejection under 35 U.S.C. §102 is improper. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 28-37 are rejected under 35 U.S.C. 102(b) as anticipated by Leung et al. (U.S. Patent 5,789,554, issued 8/4/98). The Action at Paragraph 14 asserts that the Leung et al. '554 patent discloses each and every element of the claimed subject matter. Otherwise, a rejection under 35 U.S.C. §102 would be improper.

Applicants agree that Leung et al. discloses each element of the claimed subject matter. Applicants further note that the instant application **claims priority** to USSN 08/690,102, filed 7/31/96, which resulted in the issued Leung et al. Patent 5,789,554. Since the Action clearly asserts that each element of the claimed invention is disclosed in Leung et al., then the instant application is clearly entitled to at least the priority date of USSN 08/690,102, which resulted in the issued Leung et al. '554 patent.

The Office can not have it both ways. If Leung et al. disclosed each element of the claimed invention, then the instant application is entitled to the claimed priority to the '102 application, since adequate written description must have been present in the '102 Specification to support the priority claim. Otherwise, all elements of the instant claimed invention could not have been disclosed in Leung et al., without adequate written description support. In this case, Leung et al. is not proper prior art to the instant application and the rejection should be withdrawn. Alternatively, if Leung et al. did not disclose all elements of the claimed invention, then a rejection under 35 U.S.C. §102 is improper and the rejection should be withdrawn. In either case, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 28-37 are rejected under 35 U.S.C. §102(b) as anticipated by Leung et al. (1995). Applicants respectfully assert that, for the reasons recited above, the instant claims are entitled to the August 12, 1994 priority date of USSN 08/289,576, of which USSN 08/690,102 was a continuation. Therefore, Leung et al. 1995 is not a proper prior art reference to the instant claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Priority

The instant application is a continuation of USSN 09/741,843, filed 12/22/00, which was a continuation of USSN 09/127,902, filed 8/3/98 (now U.S. Patent No. 6,187,287), which was a continuation of USSN 08/690,102, filed 7/31/96 (now U.S. Patent No. 5,789,554), which was a continuation of USSN 08/289,576, filed 8/12/94.

Support for the instant claimed subject matter may be found going back to the original priority document, USSN 08/280,576, filed 8/12/94. Figure 1 of the '576 application shows that the light chain framework regions of the humanized LL2 antibody were taken from the human REI antibody, the heavy chain FR1-FR3 were from the human EU antibody and FR4 from the human NEWM antibody.

Page 10, line 17 to pg. 11, line 13 of the 1994 Specification stated in part that,

> In general, the 3-D structure for both the mLL22 [sic] and HLL2 mAbs are best modeled by homology. The high frequency of residue identities (75.0 to 92.3%) between the deduced primary sequences of mLL2 light chain FR regions and human REI (VK) facilitates this approach because of the availability of

crystallographic data from the Protein Data Bank (citation omitted), which is incorporated by reference. Similarly, antibody EU (VH) sequences can be selected as the computer counterparts for FR1 to FR3 of the mLL2 heavy chain; FR4 was based on NEWM. As X-ray coordinate data is currently lacking for the EU sequence, NEWM structural data (PDR Code 3FAB) for FRs 1 to 4 can be used, and amino acid side groups can be replaced to correspond to mLL2 or EU (hLL2) as needed.... Potentially critical FR-CDR interactions can be determined by initially modeling the light and heavy chain variable chains of mLL2. All FR residues within a 4.5 Å radius of all atoms within each CDR can thereby be identified and retained in the final design model of hLL2.

Similarly, the '576 Specification at Page 22, lines 4-23 (Example 1) stated,

By comparing the murine variable (V) region framework (FR) sequences of LL2 to that of human antibodies in the Kabat data base (citation omitted), which is incorporated by reference, the human REI (Figure 1A, Sequence ID No. 1) and EU (Figure 1B, Sequence ID No. 2) sequences were found to exhibit the highest degree of sequence homology to the FRs of VK and VH domains of LL2, respectively. Therefore, the REI and EU FRs were selected as the human frameworks onto which the CDRs for LL2 VK and VH were grafted, respectively. The FR4 sequence of NEWM, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 heavy chain. Based on the results of computer modeling studies (Figures 2A and 2B), murine FR residues having potential CDR contacts, which might affect the affinity and specificity of the resultant antibody, were retained in the design of the humanized FR sequences (Figure 1).

Also, at Page 28, lines 18-24 the '576 Specification recited that,

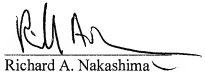
In Figure 1 (Sequence ID Nos. 1 and 2), there is compared the amino acid sequence between murine and humanized LL2 VK domains (Figure 1A) and between murine and humanized LL2 VH domains (Figure 1B). In the VK chain, human REI framework sequences were used for all FRs. In the VH chain, human EU framework sequences were used for FR 1-3, and NEWM sequences were used for FR-4.

Thus, there is ample support in the 1994 filed specification of USSN 08/280,576 for the subject matter of the pending amended claims, and Applicants submit that the instant claims are entitled to the 1994 priority date of the '576 application. Thus, none of the Leung et al. cited publications are prior art to the instant claims. Reconsideration and withdrawal of the rejections over Leung et al. are respectfully requested.

Conclusion

In light of the amendments and remarks herein, Applicants respectfully request reconsideration, withdrawal of the rejections and a finding of allowable subject matter for all pending claims. If there are any remaining questions, the courtesy of an Examiner's Interview is requested.

Respectfully Submitted,

By: 

Dated: November 30, 2006

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